UNIVERSITY OF THESSALY

SCHOOL OF MEDICINE

MSc Programme

"Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics"

Diploma Dissertation

A prospective, randomized, double- blinded, single center clinical trial to evaluate the efficacy of Lugol's iodide solution in the management of intraoperative bleeding in patients with toxic multinodular goiter undergoing total thyroidectomy.

Angeliki Chorti

Resident of General Surgery, 1st Propedeutic Department of Surgery, AHEPA University of Thessaloniki

Supervisor: **Dr. Stefanidis Ioannis**

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ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

" Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική"

Διπλωματική εργασία

Προοπτική, τυχαιοποιημένη, διπλή τυφλή κλινική μελέτη για την αξιολόγηση της αποτελεσματικότητας του διαλύματος Lugol's iodide στη μείωση της διεγχειρητικής αιμορραγίας κατά τη διάρκεια ολικής θυρεοειδεκτομής σε ασθενείς με τοξική πολυοζώδη βρογχοκήλη.

Αγγελική Χόρτη

Ειδικευόμενη Γενικής Χειρουργικής, 1η Προπαιδευτική Χειρουργική Κλινική, Π.Γ.Ν.Θ. ΑΧΕΠΑ

Επιβλέπων Καθηγητής: **κ. Στεφανίδης Ιωάννης**

Τριμελής Επιτροπή**:** *Στεφανίδης Ιωάννης, Χρυσούλα Δοξάνη, Ζιντζαράς Ηλίας*

Λάρισα, Σεπτέμβριος 2018

Πρόλογος

Η παρούσα διπλωματική εργασία εκπονήθηκε στα πλαίσια του Μεταπτυχιακού Προγράμματος "Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική". Αφορά στη συγγραφή ενός πρωτοκόλλου για τη διενέργεια παρεμβατικής κλινικής μελέτης αξιολόγησης της αποτελεσματικότητας του διαλύματος Lugol στη μείωση της διεγχειρητικής αιμορραγίας κατά τη διάρκεια ολικής θυρεοειδεκτομής σε ασθενείς με τοξική πολυοζώδη βρογχοκήλη.

Στο σημείο αυτό, θα ήθελα να ευχαριστήσω τον επιβλέποντα καθηγητή της εργασίας μου, κο Στεφανίδη Ιωάννη για την πολύτιμη συνδρομή του στην εκπόνηση της εργασίας, καθώς και τον καθηγητή κο Ζιντζαρά Ηλία για τις ανεκτίμητες γνώσεις που μου προσέφερε στον κύκλο των μεταπτυχιακών μου σπουδών. Επιπρόσθετα, θα ήθελα να ευχαριστήσω τον καθηγητή μου, κο Παπαβραμίδη Θεοδόσιο, για την αμέριστη συνδρομή του στην ανεύρεση και εκπόνηση του θέματος του πρωτοκόλλου.

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Abbreviations

aPTT; activated partial thromboplastin time

Ca^{2+}; ionized calcium

CRF; case report form

fT3; free triiodothyronine

fT4; free thyroxine

Hgb; hemoglubin

Ht; hematocrit

ICF; Informed consent form

INR; International normalized ratio

P^{+}; phosphorus

PT; prothrombin time

PTH; parathormone

TSH; thyroid stimulating hormone

WBC; white blood cells

Abstract

This is a prospective, randomized, double- blinded, single center clinical trial to evaluate the efficacy of Lugol's iodide solution in the management of intraoperative bleeding in patients with toxic multinodular goiter undergoing total thyroidectomy. The primary objective is to assess any difference in the amount of intraoperative bleeding in patients who receive preoperative Lugol's iodine before total thyroidectomy. The secondary objectives are to assess any adverse events of the agent, to evaluate the effect of other cofactors on intraoperative bleeding during total thyroidectomy, as well as the changes in thyroid ultrasound measurements after 10days therapy with Lugol's solution. 27 patients will participate in the study, separated into two groups: Group A will receive Lugol's solution, Group b will receive placebo. The study will be conducted until all subjects of each category will have included. It is estimated that it will take up to 24 months to enroll the patients. The study duration for a single patient will be 15 days. A per protocol analysis will be conducted initially.

Keywords: Lugol's solution, toxic multinodular goiter, total thyroidectomy, clinical study

1.0 Synopsis

Study title: *A prospective, randomized, double- blinded, single center clinical trial to evaluate the efficacy of Lugol's iodide solution in the management of intraoperative bleeding in patients with toxic multinodular goiter undergoing total thyroidectomy.*

Investigator: *Angeliki Chorti, MD*

Objective: *The primary objective is to assess any difference in the amount of intraoperative bleeding between patients who receive preoperative Lugol's iodine before total thyroidectomy due to toxic multinodular goiter and these who do not. The secondary objectives are to assess any adverse events of the agent as well as to evaluate the effect of other cofactors on intraoperative bleeding during total thyroidectomy.*

Population/ Sample size: *27 patients separated into two groups: Group A will receive Lugol's solution, Group b will receive placebo solution.*

Inclusion/ Exclusion Criteria:

Inclusion criteria

1) *Patients are over 18 years old*
2) *Patients scheduled for a non-emergency operation*
3) *Patients diagnosed with toxic multinodular goiter*
4) *Patients with pre- and postoperative parathormone (PTH), total serum calcium (corrected for albumin), phosphate levels within normal range.*
5) *Patient signs and dates a written informed consent form (ICF) and indicates an understanding of the study procedures*

Exclusion criteria

1) *Patient is participating in another clinical trial which may affect this study's outcomes*
2) *Patient with solitary toxic nodule*
3) *Patients with non-toxic multinodular goiter*
4) *Patient with uncertain fine-needle aspiration biopsy (indicating cancer or suspicious cytology)*
5) *Patient with previous thyroid and parathyroid operation or neck irradiation*
6) *Patients with retrosternal multinodular goiter*

7) *Patients with recurrence of multinodular goiter*
8) *Pregnancy*
9) *Refusal to participate in the study*
10) *Patient receiving anticoagulation treatment for other medical condition*
11) *Systemic diseases (e.g. infections, neoplasms, coagulation disorders)*

Design: *This study is an open, prospective, randomized, double- blinded, placebo controlled single center clinical study to evaluate the efficacy of Lugol's solution in the management of intraoperative bleeding during total thyroidectomy in patients with multinodular goiter.*

Duration: *The study will be conducted until all subjects of each category will have included. It is estimated that it will take up to 24 months to enroll the patients. The study duration for a single patient will be 15 days.*

Data analysis: *In this study, the primary analysis will be conducted according to per protocol analysis method.*

Endpoints: *In this study, the primary endpoint is the assessment of minimized intraoperative bleeding during total thyroidectomy in patients with toxic multinodular goiter after receiving Lugol's solution compared to the placebo group. The secondary outcomes are the changes in thyroid ultrasound measurements after 10days therapy with Lugol's solution, as well as the assessment of possible confounding factors that affect the intraoperative bleeding.*

2.0 Page of Signatures

Primary investigator:

Investigators:

Sponsor:

Protocol ID:

Dates:

Protocol version: *ver.1*

3.0 Background

Hyperthyroidism is a condition of excessive production and secretion of thyroid hormones, which can lead to hemodynamic variations such as increased heart rate and myocardial contractility and decreased peripheral resistance. The preoperative preparation of these patients is of great importance in order that severe intraoperative and postoperative complications, caused by the increased vascularity of the thyroid gland, are avoided. One of the most serious complications is the postoperative bleeding into the neck which can be life-threatening as it can threaten the airway. The percentage of this complication is low in experienced hands (0.25-2.3%). Furthermore, an increased intraoperative bleeding can reduce the surgeon's ability to detect the recurrent laryngeal nerve, the other vessels of the neck and the parathyroid glands. [1]

Preoperative treatment with Lugol solution before total thyroidectomy is a new method of reducing the intraoperative bleeding as well as the complications caused by increased vascularity of the gland. Lugol solution is a solution of inorganic iodine, potassium iodide and distilled water which increase the thyroid iodide uptake, blocks the synthesis and secretion of thyroid hormones (causing an acute Wolff- Chaikoff effect) and reduces the vascularization of the gland.[1-4] Although its use is widespread as an antithyroid agent, there are not enough data for the effectiveness of the method, mainly due to lack of subjective assessment of the method. In addition to this, the drug dosage and the appropriate antithyroid therapy are still controversial in the international literature. According to ATA guidelines, the recommended dosage of Lugol's solution is 5-7 drops (meaning 0.25-0.35 ml, 8mg iodide/drop) three times per day mixed with water or juice for 10 days. [5, 6]

Drug interactions [7]

- antithyroid agents -- potentiate the hypothyroid and goitrogenic effects
- captopril, enalapril, lisinopril -- causing hyperkalemia
- lithium-- potentiate the hypothyroid and goitrogenic effects

- diuretics-- causing hyperkalemia
- sodium-iodide 131(therapeutic)-- reduces the uptake of this agent

Adverse events[7]

- Allergic reactions (angioedema, arthralgia, eosinophilia, swelling of lymph nodes, urticaria) -- need medical attention, less frequent incidence[8]
- Potassium toxicity-- need medical attention, less frequent incidence
- Iodism-- need medical attention, less frequent incidence
- diarrhea -- need medical attention if persistent, less frequent incidence
- nausea, vomiting-- need medical attention if peristent, less frequent incidence[8]
- stomach pain-- need medical attention if persistent, less frequent incidence
- saliva swelling, increase in salivation, metallic taste of mouth
- rash[8]
- Jod- Basedow effect, due to prolongation of therapy [9]

Precautions[7]

- pregnancy- iodide cross the placenta and can cause thyroid dysfunction in the infant
- Breast-feeding- iodide is distributed into the milk
- Geriatrics- many co morbidities that should taken into consideration, especially renal dysfunction
- Pediatrics-- may cause skin rash

Color Doppler examination is the most reliable, non-invasive imaging technique of the preoperative assessment of the thyroid gland vascularity. Doppler is applied for the measurement of intrathyroidal blood flow as well as this of the main thyroid arteries.[4, 10]

4.0 Study objectives

4.1 Primary objective

To assess any difference in the amount of intraoperative bleeding between patients who receive preoperative Lugol's iodine before total thyroidectomy due to toxic multinodular goiter and these who do not.

4.2 Secondary objective

To assess any adverse events of the agent. To evaluate the effect of other cofactors on intraoperative bleeding during total thyroidectomy.

5.0 Study Design

5.1 Overview

This study is an open, prospective, randomized, double- blinded, placebo controlled single center clinical study to evaluate the efficacy of Lugol's solution in the management of intraoperative bleeding during total thyroidectomy in patients with multinodular goiter.

5.2 Study duration

The study will be conducted until all subjects of each category will have included. It is estimated that it will take up to 24 months to enroll the patients. The study duration for a single patient will be 15 days.

5.3 Randomization method

A simple randomization method will be applied in this study. During the initial visit, every patient will receive a serial number which will be recorded on the Case Report Form (CRF) . This number will be unique and specific for this subject and will not be reassigned to another patient. The patients will be randomly assigned to the two groups in a 1:1 ratio by a certified computer system tested by our statisticians.

5.4 Control and design

Lugol's iodide is a solution administered orally with drops. The study drugs include Lugol's solution and placebo solution. They will be stored in a tight container in a dry place between 15-30°C. The placebo drug will be manufactured identical to the Lugol's solution by a specialized pharmacist and it will be preserved by the sponsor in order that the solution administered will be unknown to the investigators.

5.5 Blinding

As this study is double- blinded, the two solutions will be identical (as mentioned above) in order that both the patients and the investigators do not know the drug administered.

6.0 Study population

6.1 Inclusion criteria

1) Patients are over 18 years old

2) Patients scheduled for a non-emergency operation

3) Patients diagnosed with toxic multinodular goiter

4) Patients with pre- and postoperative parathormone (PTH), total serum calcium (corrected for albumin), phosphate levels within normal range.

5) Patient signs and dates a written informed consent form (ICF) and indicates an understanding of the study procedures

6.2 Exclusion criteria

1) Patient is participating in another clinical trial which may affect this study's outcomes

2) Patient with solitary toxic nodule

3) Patients with non-toxic multinodular goiter

4) Patient with uncertain fine-needle aspiration biopsy (indicating cancer or suspicious cytology)

5) Patient with previous thyroid and parathyroid operation or neck irradiation

6) Patients with retrosternal multinodular goiter

7) Patients with recurrence of multinodular goiter

8) Pregnancy

9) Refusal to participate in the study

10) Patient receiving anticoagulation treatment for other medical condition

11) Systemic diseases (e.g. infections, neoplasms, coagulation disorders)

6.3 Withdrawal criteria

As it is described in the informed consent form, any patient can withdraw from the study at any time without having any personal or medical cost.

The withdrawal percentage should not exceed 10% , as a per protocol analysis of the primary objective will be conducted.

7.0 Study Procedure

Patients with toxic multinodular goiter that have an indication for surgery meeting the inclusion criteria will participate in this study after signing the inform consent form at the initial visit. Afterwards, patients will receive their unique serial number and will be randomly assigned to either Group A(Lugol Group) or Group B (placebo group). The solution will be administered to the participants ten (10) days before surgery. Patients will be strongly advised to take 5 drops of the solution three times per day for 10 days. An ultrasound will be conducted at the initial visit and at day 9 after the drug administration in order that the volume of the thyroid gland and its blood supply to be measured. The ultrasound measurements will include the superior thyroid artery blood flow, resistance index and the thyroid gland volume. After the end of 10-days Lugol treatment, patients will be operated, undergoing total thyroidectomy, by the same surgeon. Intraoperatively, the blood loss will be measured as the amount of blood in the suction bottle.

7.1 Pre-operative measurements

Procedures performed such as routine hospital examinations, antibiotic prophylactic treatment and diet will be according to the standard management protocol and will be recorded for the study. The following pre-surgery information will be recorded:

1 Demographic information including: name, age, gender, ethnicity

2 Height, weight, BMI and American Society of Anesthesiologists physical status classification system (I-VI)

3 Behavioral history (Smoking, alcohol or drug use)

4 Preoperative labs (WBC, Ht, Hgb, Ca2+, fT3, fT4, TSH, PTH, P+, PT, aPTT, INR)

5 Diagnosis including clinical observations and previous imaging results

6 Pre-operative ultra-sound characteristics of the thyroid gland (thyroid volume, blood flow, resistance index)

7 Medications

8 Current and past history of surgical and medical comorbidities

9 Any adverse events related to the solution administered

7.2 Intra-operative measurements

The surgeon will perform the preplanned operation. The following intraoperative variables will be recorded for all patients:

1 Surgery date

2 Duration of surgery

3 Operation performed

4 The amount of blood in the suction bottle

5 Procedure related comments

7.3 Pathology data form

The following pathology data will be recorded for all patients:

1 Post-operative diagnosis including pathology report

2 Weight of the thyroid gland

3 Dimensions of the thyroid gland

7.4 Postoperative measurements

Follow-up evaluation will be performed during hospitalization. The following information will be recorded:

1 Postoperative labs (WBC, Ht, Hgb, Ca2+, fT3, fT4, TSH, PTH, P+, PT, aPTT, INR)

2 Postoperative assessment of Chvostek and Trousseau signs

8.0 Complications and adverse events- discontinuation criteria

Adverse events can be any unpleasant, unintended reaction, symptom, diagnosis, vital signs, deterioration of any previous co morbidity, abnormal laboratory finding recorded at the initiation of the study or any new clinical manifestation that started coincidentally with the initiation of the study.

Serious Adverse Events include:

1 Death regardless of cause

2 Any-life-threatening event

3 Any hospitalization or prolongation of existing hospitalization

4 Any event that results in persistent or significant disability or incapacity to the patient.

Adverse reaction can be any unpleasant, unintended reaction to the investigational product related to the administered dose. An adverse reaction must be characterized by authorized medical expert as relevant (result of drug administration) or irrelevant (derives from a patient co morbidity) to the drug. Their classification as mild, moderate and severe is based on the extent of daily activities limitations.

Adverse events and reactions must be recorded in the CRF in a detailed way (what kind of event, when it started, its symptoms, the severity, the duration, if they occur prior to the initiation of the study). Sponsor must be informed for an adverse experience within 24 hours and it should be included in the security report of the drug. Investigators are obliged to keep all the security reports for specific time defined by the local regulatory authorities. Patients should be followed-up after an adverse experience until recession or stabilization, including cases of patients withdrawn from the study.

Study discontinuation criteria include safety, effectiveness and quality concerns about the drug administered. The sponsor can stop the clinical

study at any time, if there are severe concerns, by a written termination report reporting the reasons of the study discontinuation. If an investigator intent to withdraw from the study, he/she must inform the sponsor by a written report referring to the reasons of his/her withdrawal.

9.0 Statistical analysis

9.1 Endpoints

In this study, the primary endpoint is the assessment of minimized intraoperative bleeding during total thyroidectomy in patients with toxic multinodular goiter after receiving Lugol's solution compared to the placebo group. The mean difference of blood loss volume between the two groups will be compared.

The secondary outcomes are the changes (mean difference) in thyroid ultrasound measurements (the superior thyroid artery blood flow, resistance index and the thyroid gland volume) after 10days therapy with Lugol's solution, as well as the assessment of possible confounding factors that affect the intraoperative bleeding.

9.2 Sample size

A power approach for two independent groups (means) will be applied for the sample size calculation in this clinical study. The power is set at 90% and the p-value at 0.05. According to literature, the mean blood loss volume in placebo group is μ_1= 172.2 ml and SD= 96.2. A decrease in Lugol group of 50% (μ_2=86.1) is considered clinical significant. The sample size is estimated to be 27 patients.

9.3 Data analysis

The primary analysis will be conducted according to per protocol analysis.

Parametrical Independent T-test or Mann-Whitney U test will be applied to check the null hypothesis that the intraoperative blood loss is equal between two treatment groups (Lugol and placebo). Furthermore, the difference between ultrasound findings before and after the use of Lugol's solution will be assessed with parametrical paired- sample t-test or Wilcoxon test. Chi-square test or Fisher's exact test will be applied for categorical variables. Logistic regression will be performed to assess the confounding factors for intraoperative bleeding (age, gender, ethnicity,

thyroid hormones' levels, Lugol's use, preoperative thyroid volume, blood flow).

10.0 Data monitoring plan

The monitoring of the data will be accrual. All records related to the study will be kept by the investigator ,who will be responsible for them until the completion of the study. Afterwards, they will be transferred and stored in the general archive according to standards of good clinical practice.

The progress of the clinical study will be under strict supervision by the sponsor. The sponsor will be responsible for the compliance, the integrity , coherence and reliability of the data and must have access to medical files. The investigators must have frequent communication with the sponsor and inform them about all updates referring to the study.

11.0 Human subjects- Data confidentiality

11.1 Informed consent form

Prior to study institution review board (IRB) approval should be obtained. Any changes in the study protocol, informed consent forms, or investigator must be re-approved by the IRB. All patients enrolled in the study will provide their consent prior to entering the study. An informed consent form shall be signed and dated by the patient. The investigator will retain the forms as part of the study records.

This study will be executed in accordance with the Declaration of Helsinki, in agreement with the guidelines for conducting a clinical investigation in accordance with the principles of ICH GCP outlined in the E6 document. By signing the present protocol, participants in the study commit themselves to carry it out in accordance with local legal requirements.

All eligible patients should have the capacity to provide an informed consent. The above described inclusion and exclusion criteria were designed to ensure the entry of the appropriate population of patients

to this study and will be approved by the local IRB. Screening for these criteria will be conducted by the coordinator. Eligible patients will be educated about the research proposal by a study investigator. To determine whether the patient has understood the issues, he/she will be asked to describe what the research entails and whether they have any questions. All questions will be addressed prior to enrollment. The patient can refuse participation in the study at any time. A written informed consent form will be generated. For each patient, a case report form (CRF) will be completed, providing general medical information and history.

11.2 Data confidentiality

Each patient will be identified by his/her initials and a unique patient identification number. Source data will be stored with source documents. Only personnel responsible for collecting data and transcribing it into the case report forms will have access to the data. Records will remain on site in secure areas.

12.0 Publication Policy

The results of this study will be reviewed by the investigators and the sponsors for a publication. The results will not be announced to another person until the sponsor sign an agreement.

13.0 Funding

No additional funding for the execution of the present protocol is necessary. The investigators are willing to execute the present study without any additional reimbursement.

14.0 References

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